

Maintenance Requirements of L-Thyroxine in the Treatment of Hypothyroidism

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By analyzing data from 68 hypothyroid patients ranging in age from 15 to 75 years who had been maintained in a euthyroid state for at least a year with oral levothyroxine sodium therapy, we attempted to determine whether there was a correlation between L-thyroxine dose and body weight or patient age. The mean replacement dose of L-thyroxine was 186 μg a day ± 69.6 or 2.76 μg per kg of body weight a day ± 0.82 . There was a significant correlation between L-thyroxine dose and body weight ($P < .001$), but due to the small number of patients studied who were older than 65 years of age, no correlation was noted between L-thyroxine dose and age.

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Patients who have newly diagnosed hypothyroidism are frequently started on a regimen of levothyroxine sodium at a dose that is based on their clinical state. Thus, young, otherwise healthy patients are often given full replacement doses whereas older patients—those with long-standing hypothyroidism and patients with underlying cardiovascular diseases that may be aggravated by thyroid hormone therapy—are started at lower doses that are then cautiously titrated upwards. Factors such as age and body weight have been reported to affect the dose requirements for attaining a euthyroid state.¹⁻⁹

Replacement doses of 200 to 400 μg a day of L-thyroxine were routinely recommended through the early 1970s.¹ These higher doses were considered necessary to make up for the lack of triiodothyronine administration. Because, however, it is now widely recognized that a major portion of circulating triiodothyronine results from the peripheral monodeiodination of L-thyroxine, these earlier dosage recommendations offer no therapeutic advantage and often produce a toxic effect.² Thyroid-stimulating hormone (thyrotropin) radioimmunoassay, a more sensitive indicator of euthyroidism, confirms euthyroidism when doses of 100 to 200 μg a day of L-thyroxine are administered.

Age and body weight appear to be important determinants of thyroxine requirements, though the exact effect of these variables is unclear. Investigators have not evaluated the effects of weight but have reported doses in micrograms per kilogram a day, suggesting a correlation between dosage and weight.³⁻⁵ Nilsson and co-workers in 1977 reported that L-thyroxine requirements did not correlate with body weight⁶ while other investigators^{1,7} found significant correlations. Similar dosage relationships have been noted with age.^{1,7-9} Elderly patients appear to have reduced thyroxine requirements,⁷ whereas increased requirements (3.5 to 3.8 μg per kg a day) have been found in the pediatric population.^{8,9} Thus, the effects of weight and age on adult L-thyroxine requirements need further clarification. The following study was undertaken to evaluate such effects.

Patients and Methods

The files of one clinician (F.S.G.) were reviewed for patients meeting the following criteria:

- their hypothyroidism is due to Hashimoto's thyroiditis, radioiodine therapy, thyroidectomy, radiation exposure or an idiopathic cause;

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- they are receiving thyroid replacement rather than nodule suppression therapy;
- hypothyroidism has been documented based on their clinical state and serum thyroxine and thyrotropin values before initiation of therapy;
- euthyroidism has been maintained by a constant L-thyroxine dosage regimen for at least a year, and
- there has been no known administration of drugs or coexisting disease states known to alter thyroid function or laboratory values.¹⁰

A total of 68 patients met the criteria for inclusion in the analysis. For each patient, data recorded during retrospective review of the chart included diagnosis, age, weight, sex, L-thyroxine dose and serum thyroxine and thyrotropin values. Data were analyzed using the Statistics Package for Social Sciences (McGraw-Hill) at the University of California, San Francisco, Computer Center.

Results

The charts of 13 men and 55 women were reviewed. Table 1 shows the population data. The most common cause for the hypothyroidism was radioiodine therapy followed by thyroidectomy, Hashimoto's thyroiditis, idiopathic hypothyroidism and radiation exposure.

Table 2 shows the clinical data obtained from the chart review. All patients were clinically euthyroid. The mean dose of L-thyroxine for this patient population was 186 μg a day \pm 69.6 (standard deviation [SD]). When calculated on a weight basis, the value was 2.76 μg per kg a day \pm 0.82 (SD), or 1.25 μg per lb a day.

Figures 1 and 2 show the results of the regression analysis. When dose was evaluated as a function of

body weight, the correlation coefficient was .56 ($P < .001$). The correlation coefficient for dose as a function of age was $-.11$ ($P > .05$). Body weight did not significantly decrease with age in this population ($r = -.102$, $P > .05$).

Discussion

Most investigators have found that the majority of hypothyroid patients can be maintained on a regimen of L-thyroxine at doses of 100 to 200 μg a day. Our findings support this.

The results of the present study are in agreement with those of Stock and associates (1974) and Rosenbaum and Barzel (1982) concerning the effect of body weight on dose.^{1,7} L-Thyroxine requirements increased significantly with total body weight. Our value of 2.76 μg per kg a day is slightly higher than that found by

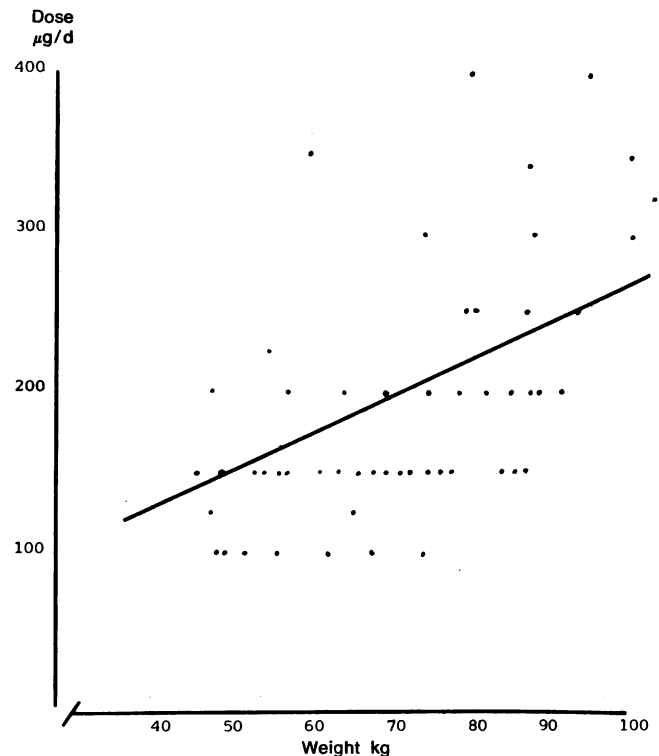


Figure 1.—Correlation between L-thyroxine dose and weight: There was a significant correlation between L-thyroxine dose and body weight, $r = .56$ ($P < .001$).

TABLE 1.—Patients Being Treated With Levothyroxine Sodium for Hypothyroidism

No. of Patients (sex)	68 (13 ♂, 55 ♀)
Age, years* (range)	37 \pm 15 (range, 15 to 75)
Weight, kg*	66.9 \pm 14.3 (range, 46 to 100)
Cause of hypothyroidism (Number of Patients)	
Radioiodine therapy	21
Thyroidectomy	20
Hashimoto's thyroiditis	19
Idiopathic	5
Irradiation	3

*Mean \pm standard deviation.

TABLE 2.—Clinical Data for 68 Patients With Hypothyroidism Being Maintained on Levothyroxine Therapy

Number of Patients	Final Serum Thyroxine Level		Final Serum TSH Level		Mean Dose $\mu\text{g}/\text{kg}/\text{d}$
	Mean \pm SD	Normal	Mean \pm SD	Normal	
68	11.3 \pm 2.3	5-12			
29			<2.00	} <10	
39			4.54 \pm 1.85		
68					186 \pm 69.6 (2.76 \pm 0.82)

TSH = thyroid-stimulating hormone (thyrotropin), SD = standard deviation

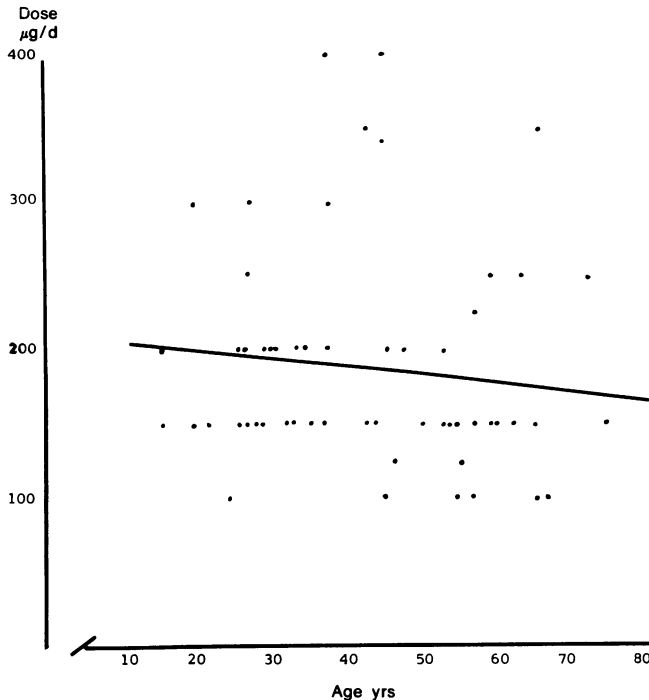


Figure 2.—Correlation of dose and age: There was no significant correlation between dose and age, $r = -.11$ ($P > .05$).

other investigators (1.86 to 2.25 μg per kg a day). Two possible explanations may account for this higher value:

First, dosage adjustments of 50- μg increments were commonly made in these patients. Even though they were euthyroid, the effect of smaller dosage increments such as 25 μg could not be determined from this study. It is possible that euthyroidism could still be maintained if smaller adjustment increments were used, though our criteria may not be sensitive enough to discriminate between doses differing by only 25 μg or less.

Second, seven of our patients were noted to require doses of more than 4 μg per kg a day. All were euthyroid as defined above and no reason for the increased requirements could be determined. Possibilities include noncompliance and erratic thyroxine absorption, which may range from 50% to 90%.¹¹

The turnover rate of L-thyroxine decreases with age due to decreases in both the distribution space after 60 years and the fractional turnover up to age 70 years of age, so that the net result is a 50% reduction in thyroxine degradation between the ages of 20 and 80 years.^{12,13} No effect of age on L-thyroxine requirements was demonstrated in this population. The patients studied by Rosenbaum and Barzel⁷ showed a significant decrease in dosage requirements continuously with age. However, their population also showed a decrease in body weight with age, the effects of which were not ruled out in the regression of dose with age. When their patients were separated into groups of younger and older than 65 years of age, a significant difference in

dosage requirements was seen (2.09 and 1.86 μg per kg a day, respectively).

There are several possible explanations for the differences between the results of their study and those of the present one. First, the present population did not show a continuous decrease in weight with age, which may have affected the results of Rosenbaum and Barzel.⁷ Second, the present population included only five patients older than 65 years, so that a comparison of an older with a younger group is not possible. It may be that the effect of age only becomes clinically significant after age 65. Last, the dose differences cited above would represent a 16- μg -a-day dose difference in a person weighing 70 kg. The sensitivity of current diagnostic tests to pick up this difference could not be evaluated in this study.

In conclusion, L-thyroxine requirements in the present population were significantly correlated with total body weight. No effects of age were noted, however, due to the small sample studied. Further investigations are required to determine which adult age groups show clinically significant differences in L-thyroxine requirements.

Addendum

The dosage recommendations in this report are based on tablets of L-thyroxine (Synthroid) manufactured before 1983 by Flint Laboratories division of Travenol Laboratories, Inc. In 1983 the tablet was reformulated to allow assay with high pressure liquid chromatography. This resulted in 100% bioavailability compared with the previous tablet, which had only 78% of expected potency.^{14,15} Thus, when using the new tablets, a dosage reduction of 20% to 30% may be necessary to maintain euthyroidism and to prevent clinical toxicity.

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